REMARKS

STATUS OF THE CLAIMS

Claims 66-71 and 125-128 were pending. Claim 66 has been amended as shown above to make explicit what is implicit in the recitation "library," namely that there are at least two different inserts in the polynucleotides of the claimed library.

35 U.S.C. § 103(a)

Claims 66-71 and 125-128 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Clontech in view of U.S. Patent No. 5,635,355 (hereinafter "Grosveld"). (Final Office Action, pages 2-6 and Advisory Action, page 2). While it was acknowledged that Clontech does not disclose a library where each and every polynucleotide has an insert that consist essentially of accessible regions of cellular chromatin, it was alleged that Grosveld provides the motivation to modify Clontech to clone regulatory sequences. *Id.*

In response to Applicants' arguments that Grosveld contains no suggestion as to libraries made by the claimed methods, it was asserted (Advisory Action, page 2):

> It appears that applicant's arguments are on the ground that the cloning in Grosveld involves cloning a single sequence (i.e. "the target sequence") and a collection of the same polynucleotide molecules is not a library. This is not found persuasive. Firstly, in a reasonably broad sense, a collection of the same polynucleotide molecules is also a library which meets the definition of the term defined in the instant specification as "a population of DNA fragments that have been propagated in some type of cloning vector." See paragraph [0198] of the published application. This is akin to a collection of 100 the same books in a room for people to read. This collection of books is still a library albeit maybe a small and limited library, but it is still library in the reasonably broad sense.

Furthermore, the Examiner again alleged that the references somehow provide the motivation to arrive at the claimed libraries (Advisory Action, page 2):

> Secondly, as set forth in the previous Office action such as on page 6 of the final rejection mailed 12/8/09, one of ordinary skill in the art would have been motivated to modify the method of Clontech and motivated by Grosveld et al. to treat the chromatin with the method of Grosveld et al. and not only clone the DNase I hypersensitive fragment from a readily made clone containing such

> fragment if the clone is available, but also to clone the DNase I hypersensitive fragments directly from the fragments identified in column 8 if there are no clones readily available comprising such fragments in order to obtain such fragments which contain regulatory sequences because Grosveld et al. claim and suggest obtaining such fragments. A collection of clones containing these different fragments (which are DNaseI hypersensitive and hence the accessible regions) would also be a library.

The Examiners assertions are all untenable.

First, the Examiner errs in asserting that the definition of a library includes multiple copies of the same thing. There is no reasonable definition of "library" that includes a collection of the same polynucleotides. A collection of the same polynucleotide is a colony or a clonal collection, not a library. Furthermore, in light of the foregoing amendment making it explicit that the library includes at least two different inserts, the Examiner's arguments are obviated.

Secondly, the Examiner errs in asserting that Grosveld and Clontech suggest a library as claimed that is obtained by the specific, recited steps, including (a) contacting cellular chromatin with a probe that cleaves the chromatin at accessible regions of cellular chromatin; (b) deproteinizing the cleaved chromatin; (c) digesting the deproteinized chromatin with a nuclease to generate a collection of polynucleotide fragments; and (d) selectively cloning polynucleotide fragments comprising one end generated by probe cleavage.

In fact, there is no combination of Grosveld and Clontech that teaches or suggest libraries as claimed. Clontech is silent as to libraries where all the inserts of the library consist essentially of accessible regions. At best, Grosveld states that hypersensitive sites may be "mapped" (col. 7, lines 59-63). The only cloning referred to in Grosveld involves construction of a single target sequence that, in certain cells, comprises a DNAse hypersensitive site. The often-referred to col. 8 of Grosveld does not teach cloning of fragments as recited in the claims. Grosveld teaches (at column 8) that, in one case, nuclei were treated with DNase I (first enzyme), then deproteinized DNA was recut with *Asp*718 or *Bgl*II (second enzymes). *See,* Grosveld, column 8, lines 17-32. In a second case, nuclei were treated with DNase I (first enzyme), and deproteinized DNA was recut with *Bam*HI (second enzyme). *See,* Grosveld, column 8, lines 34-41. However, nowhere does Grosveld suggest that these fragments are cloned to make a library. To the contrary, the portions of Grosveld from column 15 (cited by the Examiner), the DNA fragments that are cloned are an *Xba*I-*Xba*I fragment (containing DNaseI HS1), a *Hind*III-*Hind*III fragment

(containing DNaseI HS2), a *Asp*718-*Sal*I fragment rendered blunt-ended (containing DNaseI HS3) and a partial *Sac*I fragment (containing DNaseI HS4). *See,* Grosveld, column 15, lines 16-31. Notably, none of these fragments which Grosveld teaches or suggests should be cloned correspond to a DNaseI-*Asp*718 fragment, a DNaseI-*Bgl*II fragment or a DNaseI-*Bam*HI fragment, as described in column 8 of Grosveld.

Thus, the portions of Grosveld cited by the Examiner do not teach the cloning of a collection of fragments that have been produced by contacting nuclei with a first enzyme, deproteinizing and contacting the deproteinized DNA with a second enzyme, as claimed.

The Examiner has also improperly failed to consider that the Board of Patent Appeals and Interferences has previously determined that Examiner's assessment of what Grosveld teaches is in error. In particular, in the parent case (now U.S. Patent No. 7,217,509), the Board determined that Grosveld does not teach or suggest cloning of fragments obtained by as recited. *See,* Decision on Appeal mailed December 21, 2006 in Appeal No. 2006-2851 (Application No. 09/844,501), pages 3-4, underlining in original:

> Upon review of the disclosure of Grosveld, we do not find that the examiner has provided sufficient evidence to support a prima facie case of obviousness of the method of claim 123 [claim 1 of issued patent]. ...
>
> Grosveld at column 8, lines 16-32, described deproteination steps and digestion with a second enzyme to generate fragments, such as BglII, consistent with steps (c) and (d) of claim 123. Then, "the exact location of the DNaseI hypersensitive site[s] of the 3' adult β-globin gene were determined using two single copy DNA probes and several restriction enzyme digests of DNaseI digested HEL nuclei. The data summarized in FIG. 2 (A-D) show that there is a single DNaseI hypersensitive site between the 2.3 kb BglII fragment and the 2.4 kb HindIII fragment...." Column 8, lines 48-51. Accordingly, Grosveld obtained fragments of the adult β-globin gene and probed these fragments to locate the DNaseI hypersensitive sites. Grosveld did not, according to claim 123, step (e), contact the DNA fragments obtained in step (d) with a population of vector molecules, wherein the vector molecule comprise a first end that is compatible with the first enzyme and a second end that is compatible with the second enzyme, under conditions favorable to ligation of compatible ends; or step (f), select polynucleotides comprising a DNA fragment <u>ligated to a vector molecule</u>. Grosveld, on the other hand, probed DNA fragments which were not ligated to a vector, and selected the DNA fragment of interest having the DNaseI hypersensitive site by its ability to bring to a probe.

The Board also confirmed that the fragments "cloned" at column 15 of Grosveld are not inserts as claimed. *See,* Decision on Appeal mailed December 21, 2006 in Appeal No. 2006-2851 (Application No. 09/844,501), pages 4-5, emphasis added:

> In a different experiment, Grosveld incorporated the previously identified DNaseI hypersensitive sites into a vector or plasmid containing both the hypersensitive sites and the adult β-globin gene. Column 15, lines 6-47. **The DNA fragments cloned in the experiment described in column 15 are not the same fragments described in column 8.** In particular, the hypersensitive sites (HSS)-containing fragments cloned in col. 15 are not the DNAseI restriction enzyme fragments from col. 8. See col. 15, lines 45-46: PvuI-BstEII fragment with HSS 1 and 2; BstEII-ClaI fragment with HSS 3 and 4.
>
> In contrast, appellants describe their method in the specification, pages 49-50, as follows. ...
>
> For the reasons discussed herein, we do not find the examiner has provided sufficient evidence to support a prima facie case of obviousness. The rejection of claims over Grosveld is reversed.

Thus, for the reasons set forth in the Board decision regarding the parent application, Grosveld does not teach or suggest step (d) of the instant claims, namely selective cloning of fragments generated as claimed. As such, the claimed libraries are necessarily different in structure (by virtue of the inserts) from the single clones described in Grosveld.

In addition, in the parent case, the Board determined that there was no combination of Grosveld and additional references, including the NEB restriction enzyme catalog, which teaches the step of selective cloning. *See,* Decision on Appeal mailed December 21, 2006 in Appeal No. 2006-2851 (Application No. 09/844,501), page 6:

> With respect to the other pending obviousness rejections before us, all rejections stand or fall on the relevance of Grosveld to the pending claims. The examiner relies on the NEB catalog ...
>
> We do not find that either NEB catalog, Li or Chung overcome the above noted deficiency of Grosveld and its failure to teach steps (e) and (f) of claim 123, and therefore the rejections for obviousness over Grosveld taken with NEB catalog, Li or Chung are reversed.

In sum, for the reasons of record and as set forth by the Board in the parent application, Grosveld does not teach libraries as claimed because this reference fails entirely to teach selective cloning of fragments (inserts) obtained as recited in the pending claims. Accordingly, a

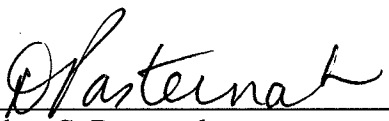
prima facie case of obviousness has not been and cannot be established and the rejection of these claims as allegedly obvious over the cited references should be withdrawn, and these claims should be allowed.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

Respectfully submitted,

Date: April 8, 2010

By: 

Dahna S. Pasternak
Attorney for Applicant
Registration No. 41,411

ROBINS & PASTERNAK LLP
1731 Embarcadero Road, Suite 230
Palo Alto, CA 94303
Tel.: (650) 493-3400
Fax: (650) 493-3440